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(57) Abstract

The present invention pertains to the use of inhibitors of phosphodiesterase I for the treatment of urinary bladder diseases, in particular the use of vincamine, vinpocetine (ethyl apovincamin-22-oate), and/or modified compounds of the said inhibitors having inhibiting properties for PDE I, as well as pharmacologically compatible salts thereof, in local and systemic administration.

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USE OF PDE INHIBITORS IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF BLADDER DISEASES

The present invention pertains to the use of inhibitors of phosphodiesterase I (PDE I) for the treatment of urinary bladder diseases.

The physiological transmission of information for the relaxation of smooth muscle cells is effected by transmitters (messengers) of the blood (hormones) or the nerves (neurotransmitters). These messengers and neurotransmitters cause an increase in the levels of the cyclic nucleotides "cyclic adenosine monophosphate" (cAMP) and "cyclic guanosine monophosphate" (cGMP) in the smooth muscle cell, resulting in relaxation. cAMP and cGMP themselves are hydrolyzed by phosphodiesterases (PDEs). Inhibitors of the PDEs in turn reduce the hydrolyzation of cAMP and cGMP, resulting in an increase of these molecules within the cell and thus in a relaxation of the smooth muscle cell. This mechanism of action has been described, for instance, by C.D. Nicholson, R.A. Challiss, and M. Shadid: Pulm. Pharmacol. 7 (1) (1994), 1-17, and T.J. Torphy et al.: J. Pharmacol. Exp. Ther. 265 (3) (1993), 1213-23.

From these publications as well as from W.J. Thompson: Pharmacol. Ther. 51 (1991), 13-33, and J. Beavo in: J. Beavo and M.D. Housley (eds.): Cyclic nucleotide phosphodiesterases: Structure, regulation and drug action, Chichester, New YorkBrisbane-Toronto-Singapore, Wiley, 1990: 3-15; there is further known the distinction of a number of isoenzymes of PDEs is distinguished between five

different PDEs (I - V) which are differently distributed in the individual organs and organ systems and have different activities according to their distribution. In the publications mentioned, there is also discussed the occurrence of the different isoenzymes in various tissues.

An interesting target for the use of PDE isoenzyme selective inhibitors is the lower urinary tract since the pharmacological therapy of bladder dysfunctions with conventional substances is often little effective and limited by side-effects. Therefore, a well-aimed effect on the bladder muscle by inhibiting a functionally important PDE isoenzyme appears to be superior to established pharmacological treatment modalities.

According to the invention it has surprisingly been found that inhibitors of phosphodiesterase I in the preparation of a drug can be used in the treatment of urinary bladder diseases. Preferred embodiments of the use according to the invention are related with claims 1 - 4. The claim 5 deals with a method for treating urinary bladder diseases by administering an inhibitor of PDE I in a sufficient amount to a patient in need thereof. It is preferred that the formulation is given in a galenically acceptable formulation.

According to the invention a method of identifying and classifying inhibitors of PDE I is disclosed by competitive studies using inhibitors of PDE I as competing agents.

Surprisingly, it has now been found that PDE I is of particular importance in human bladder muscle: A well-aimed inhibition of this isoenzyme will result in relaxation of the bladder muscle even if minute doses of an inhibitor are administered, e.g., the PDE I inhibitor vinpocetine in a dosage of 10^{-5} mol/l (figure 2), with no appreciable effects to other organs, in particular to vessels. Therefore, there is an excellent efficacy and potency in the treatment of urinary bladder diseases.

Therefore, the subject matter of the invention is the use of PDE I inhibitors in the treatment of urinary bladder diseases, in particular the so-called urge symptoms, frequency, urge incontinence, involuntary discharge of urine, and instabilities of the bladder muscle (detrusor instability), and the use of the inhibitors for the preparation of drugs useful for this purpose as well as drugs containing PDE I inhibitors for the objects mentioned.

Preferred inhibitors of PDE I are:
vincamine, vinpocetine (ethyl apovincamin-22-oate),
and/or modified compounds of the said inhibitors having inhibiting properties for PDE I,
as well as pharmacologically compatible salts thereof.

The pharmacologically compatible salts are obtained in a similar manner by neutralizing the bases with inorganic or organic acids. As inorganic acids, there may be used, for example, hydrochloric acid, sulfuric acid, phosphoric acid or hydrobromic acid, and as the organic acids, for example, carbonic, sulfo or sulfonic acids, such as acetic acid, tartaric acid, lactic acid, propionic acid, glycolic acid, malonic acid, maleinic acid, fumaric acid, tannic acid, succinic acid, alginic acid, benzoic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, cinnamic acid, mandelic acid, citric acid, malic acid, salicylic acid, 3-aminosalicylic acid, ascorbic acid, embonic acid, nicotinic acid, isonicotinic acid, oxalic acid, amino acids, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid, or naphthalene-2-sulfonic acid.

In the preparation of the drugs for the treatment of the diseases mentioned, an effective amount of the PDE I inhibitors or salts thereof is used in addition to the usual excipients, vehicles, and additives. The dosage depends on the species, body weight, age, individual condition, and type of administration.

Possible forms of application are oral, intravenous, intra-

muscular, subcutaneous, and intraluminal (e.g. intrasvesical) formulations. The latter are, in particular, solutions and formulations as used for parenteral administration as well.

Formulations for parenteral administration will range from 0.05 μg to 100 mg, preferably from 1 mg to 50 mg, of the compounds mentioned per unit dose and may be present in separate unit dose forms, such as ampoules or vials. Preferably, solutions of the active ingredient are used, more preferably aqueous solutions, and mainly isotonic solutions, but also suspensions. These injection forms may be provided as a ready preparation, or they may be formulated only immediately before use by admixing the effective compound, for example, the lyophilizate, optionally with other solid carriers, with the solvent or suspension medium desired.

For oral administration, there are used the usual galenic preparations, such as tablets, coated tablets, capsules, dispersible powders, granules, aqueous or oily suspensions, syrups, liquors, or drops.

Solid preparations may contain inert excipients, additives and vehicles, such as calcium carbonate, calcium phosphate, sodium phosphate, lactose, starch, mannitol, alginate, gelatin, guar gum, magnesium or aluminium stearate, methylcellulose, talcum, highly dispersed silicic acids, silicone oil, higher-molecular fatty acids (such as stearic acid), gelatin, agar-agar, or vegetable or animal fats and oils, solid high-molecular polymers (such as polyethylene glycol); formulations useful for oral administration may optionally contain additional flavoring and/or sweetening agents.

Liquid preparations may be sterilized and/or may optionally contain additives, such as preservatives, stabilizers, wetting agents, penetration agents, emulsifiers, spreading agents, solubilizers, salts for adjusting the osmotic pressure or for buffering, and/or viscosity modifiers.

Such additives are, for instance, tartrate and citrate buffers, ethanol, complexing agents (such as ethylenediaminetetraacetic acid and its non-toxic salts).

For adjusting the viscosity, there may be used high-molecular polymers, such as, for example, liquid polyethylene oxide, carboxymethylcelluloses, polyvinylpyrrolidones, dextranes, or gelatin. Solid vehicles are, for instance, starch, lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acids, higher-molecular fatty acids (such as stearic acid), gelatin, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats, solid high-molecular polymers (such as polyethylene glycol).

Oily suspensions for parenteral or topical (in this case intravesicular) administrations may contain vegetable, synthetic or semisynthetic oils, such as, for instance, liquid fatty acid esters having from 8 to 22 carbon atoms in the fatty acid chains, for example, palmitic, lauric, tridecylic, margaric, stearic, arachic, myristic, behenic, pentadecylic, linolic, elaidic, brassidic, erucic or oleic acids, which may be esterified with monohydric to trihydric alcohols having from 1 to 6 carbon atoms, such as, for instance,

methanol, ethanol, propanol, butanol, pentanol, or isomers thereof, glycol, or glycerol. Such fatty acid esters are, for instance, commercially available miglyols, isopropyl myristate, isopropyl palmitate, isopropyl stearate, PEG 6-caprate, caprylates/caprates of saturated fatty alcohols, polyoxyethylene-glycerol trioleates, ethyl oleate, waxy fatty acid esters, such as synthetic duck uropygial fat, coconut oil fatty acid isopropyl ester, oleic acid oleyl ester, oleic acid decyl ester, lactic acid ethyl ester, dibutyl phthalate, adipic acid diisopropyl ester, polyol fatty acid ester, etc. Also useful are silicone oils of various viscosities or fatty alcohols, such as isotridecyl alcohol, 2-octyldodecanol, cetylstearyl alcohol or oleyl alcohol, fatty acids, such as oleic acid. Further, vegetable oils, such

as castor oil, almond oil, olive oil, sesame oil, cottonseed oil, peanut oil or soybean oil, may be used. The materials mentioned have the additional property of a spreading agent, i.e. there will be a particularly good spreading on the skin.

As solvents, gelling agents and solubilizers, there may be used water or water-miscible solvents, for example alcohols, such as ethanol or isopropyl alcohol, benzyl alcohol, 2-octyldodecanol, polyethyleneglycols, phthalates, adipates, propylene glycol, glycerol, dipropylene or tripropylene glycol, waxes, methyl-cellosolve, cellosolve, esters, morpholines, dioxane, dimethyl-sulfoxide, dimethylformamide, tetrahydrofurane, cyclohexanone, etc.

As film-forming agents, there may be used cellulose ethers which can dissolve or swell both in water and in organic solvents and will form a kind of film after drying, such as hydroxypropyl-cellulose, methylcellulose, ethylcellulose, or soluble starches. Mixed gelling and film-forming agents are also possible. In this case, there are chiefly used ionic macromolecules, such as sodium carboxymethylcellulose, polyacrylic acid, polymethacrylic acid, and salts thereof, sodium amylopectine semiglycolate, alginic acid or propylene glycol sodium salt, gum arabic, xanthan gum, guar gum or carrageen.

As additional formulation aids, there may be used: glycerol, paraffins having different viscosities, triethanolamine, collagen, allantoin, novantisolic acid, perfume oils.

The use of surfactants, emulsifiers or wetting agents may also be required for the formulation, such as, for example, sodium lauryl sulfate, fatty alcohol ether sulfates, disodium N-lauryl β-iminodipropionate, polyoxyethylated castor oil, or sorbitan monooleate, sorbitan monostearate, cetyl alcohol, lecithin, glycerol monostearate, polyoxyethylene stearate, alkylphenol polyglycol ether, cetyltrimethylammonium chloride, or monoalkyl/dialkyl polyglycol ether ortho-phosphoric acid monoethanolamine

salts.

Stabilizers, such as montmorillonites or colloidal silicic acids, for the stabilization of emulsions or for preventing decomposition of active substances, such as antioxidants, for example, tocopherols or butylhydroxyanisol, or preservatives, such as p-hydroxybenzoic acid ester, may also be required for the preparation of the formulations desired.

For promoting penetration, intravesicular formulations preferably contain highly compatible organic solvents, such as ethanol, methylpyrrolidone, polyethylene glycol, oleyl alcohol, octanol, linolic acid, triacetin, propylene glycol, glycerol, solketal, or dimethylsulfoxide.

The preparation, filling and sealing of the preparations is done under the usual antimicrobial and aseptic conditions. For topical or transdermal application as well, the preparations are preferably packed in separate unit doses for easy handling, if required for stability reasons, as with parenteral forms, also by separately packing the active ingredients or their combinations as lyophilizates, optionally with solid carriers, and the solvents required etc.

Example 1 - Injection

Fifty milligrams of vinpocetine are dissolved in distilled water together with 750 mg of NaCl, the pH is adjusted to 3.7 with 1 N HCl, distilled water is added to give a total of 100 ml, and the solution is packed in 0.5 ml ampoules.

Example 2 - Solution for Topical Administration

From 500 mg of vinpocetine, 2 ml of isopropyl myristate and 10 ml of ethanol, a solution for topical administration is prepared and packed in unit doses of 2 ml each.

The efficacy and potency of the drugs according to the teaching of the invention is demonstrated by the following pharmacological studies:

Human urinary bladder muscles freshly collected in the course of an operation is cut into small strips (about 3 x 3 x 6 mm). The latter are then installed in an organ bath containing a nutrient solution ensuring survival of the organic strips. By coupling the organic strips to a measuring element, length and force changes of the organic strip can be recorded, and thus actions of compounds added to the organ bath nutrient solution can be examined through the length and force changes (increase or decrease) of the organic strip. At the beginning of the experiment, the organic strips are contracted with an appropriate standard compound (e.g., carbachol). After the contraction of the organic strips is completed, an inhibitor of phosphodiesterase I is now added in incremental dosage (10^{-9}, 10^{-8}, 10^{-7} etc. mol/l) to the organ bath solution, and the relaxation triggered thereby is measured. The results obtained are essentially applicable to the whole organism since human tissue had been used and the metabolic processes studied proceed faster in the whole organism and thus the compounds will act even more pronounced.

Figures 1 to 6 illustrate the results of these organ bath experiments.

Figure 1 shows the relaxing effect of cumulatively increasing concentrations of papaverine, an non-specific phosphodiesterase inhibitor, on human detrusor strips precontracted with 1 μM carbachol. The curve shows the average values of measurements each performed on 12 detrusor strips. This no drug, because of its severe side-effects due to interaction with all PDEs.

Figure 2 shows the relaxing effect of cumulatively increasing concentrations of vinpocetine, an inhibitor of PDE I, on human detrusor strips precontracted with 1 μM carbachol. The curve shows the average values of measurements each performed on 12 detrusor

strips.

Figure 3 shows the relaxing effect of cumulatively increasing concentrations of milrinone, an inhibitor of PDE III, on human detrusor strips precontracted with 1 μM carbachol. The curve shows the average values of measurements each performed on 10 detrusor strips.

Figure 4 shows the relaxing effect of cumulatively increasing concentrations of rolipram, an inhibitor of PDE IV, on human detrusor strips precontracted with 1 μM carbachol. The curve shows the average values of measurements each performed on 8 detrusor strips.

Figure 5 shows the relaxing effect of cumulatively increasing concentrations of zaprinast, an inhibitor of PDE V, on human detrusor strips precontracted with 1 μM carbachol. The curve shows the average values of measurements each performed on 10 detrusor strips.

Figure 6 shows the relaxing effect of cumulatively increasing concentrations of dipyridamole, an inhibitor of PDE V, on human detrusor strips precontracted with 1 μM carbachol. The curve shows the average values of measurements each performed on 10 detrusor strips. Inhibitors of PDE II have not been known to date and therefore could not be tested.

The proof as to whether a compound is suitable for the purpose according to the invention, i.e. is an inhibitor of PDE I, is furnished by known methods, such as described by Galwan et al., Arch. Pharmacol. 1990, 342, 221-227; or Nicholson, Br. J. Pharmacol. 1989, 79, 889-897; for example, according to the following general procedure:

Fresh tissue obtained during an operation is homogenized and then ultracentrifuged. Next, the supernatant is filtered, pipetted off and chromatographed. The determination of PDE isoenzymes is

performed as described in M. Truss et al.: Urology 45(5): 893-901, 1995. The determination of the amount of radioactivity permits to calculate the enzyme activity in pmol/ ml/min. A plot of the activity curve allows to identify fractions in which the phosphodiesterase activity is particularly high. The phosphodiesterase activity of each of the peaks exhibits a different composition with respect to the activity of the different substrates. This special composition of the phosphodiesterase activity allows for the assignment to a phosphodiesterase isoenzyme (PDE). A substance is considered as PDE inhibitor if the concentration thereof which is necessary for inhibiting 50% of the substrate hydrolysis (IC_{50}) is at least 20 times lower in the respective peak fraction containing the correspoonding phosphodiesterase isoenzyme than in other peak fractions. For this purpose, enzyme preparations are again carried out, as described above. Now, however, the compound to be tested is added prior to the incubation of the enzyme mixtures according to peak fractions. Then, renewed determination and plotting of the enzyme activity allows to identify a substance as being an inhibitor of the phosphodiesterase isoenzyme according to the above-mentioned definition.

C L A I M S :

1. Use of inhibitors of phosphodiesterase I in the preparation of a drug for the treatment of urinary bladder diseases.

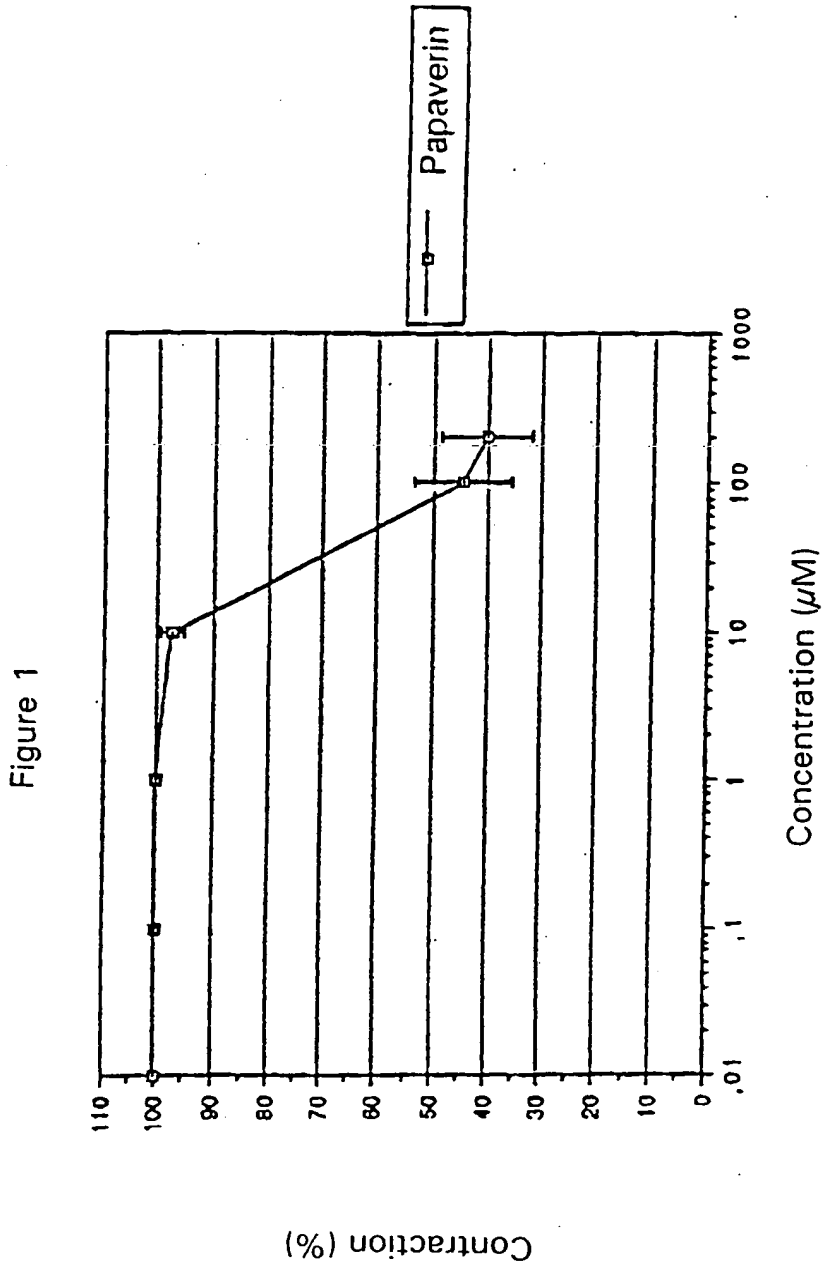
2. Use according to claim 1 for the treatment of urge symptoms, frequency, urge incontinence, involuntary discharge of urine, and instabilities of the bladder muscle (detrusor instabilities).

3. Use according to claim 1 wherein the inhibitor of phosphodiesterase I is
vincamine, vinpocetine (ethyl apovincamin-22-oate),
and/or modified compounds of the said inhibitors having inhibiting properties for PDE I,
as well as pharmacologically compatible salts thereof for treatment according to claim 1.

4. The use according to any of claims 1 through 2 in local or systemic administration.

5. A method for treating urinary bladder diseases by administering to a patient in need an inhibitor of PDE I in a sufficient amount, optionally in a galenically acceptable formulation.

6. A method of identifying and classifying inhibitors of PDE I by competitive studies using as competing agents of the PDE I the following compounds
vincamine, vinpocetine (ethyl apovincamin-22-oate),
and/or modified compounds of the said inhibitors having inhibiting properties for PDE I,
as well as pharmacologically compatible salts thereof.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Contraction (%)
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30
20
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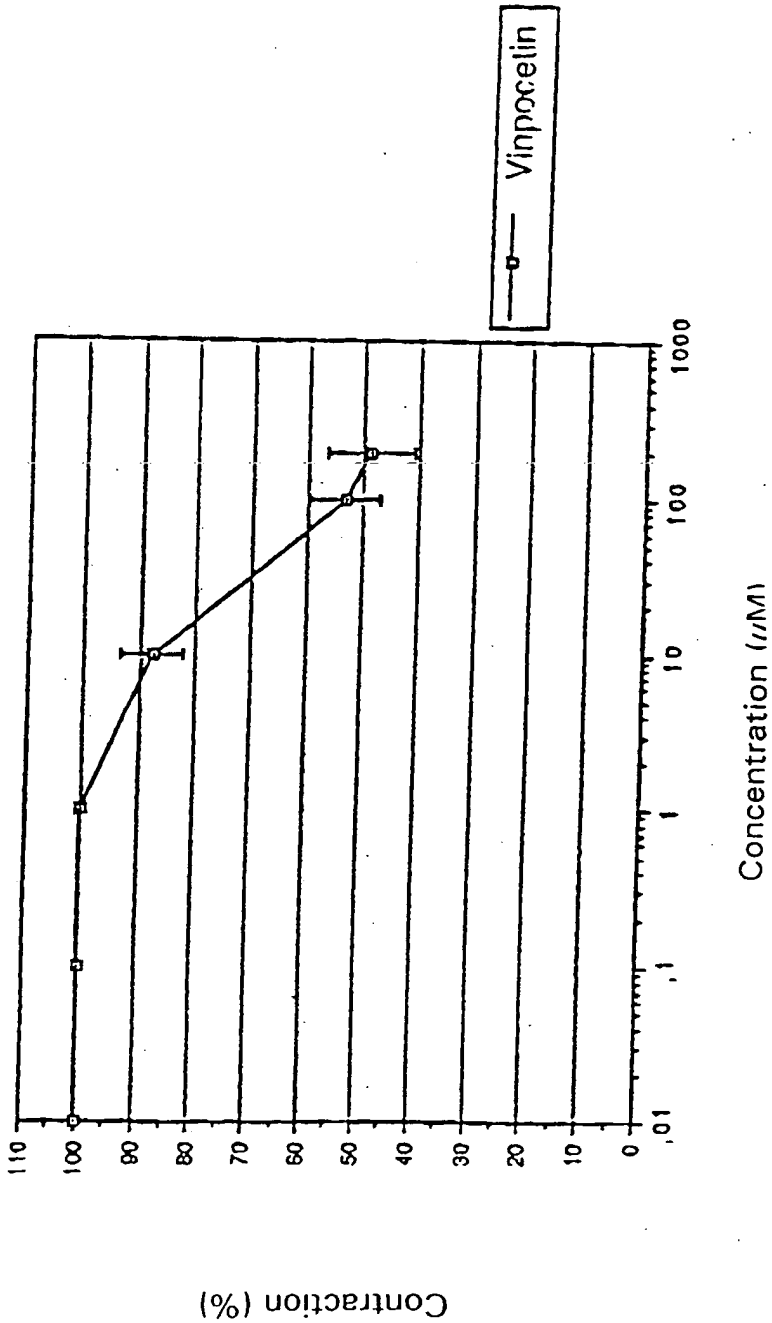
Figure 1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Contraction (%)
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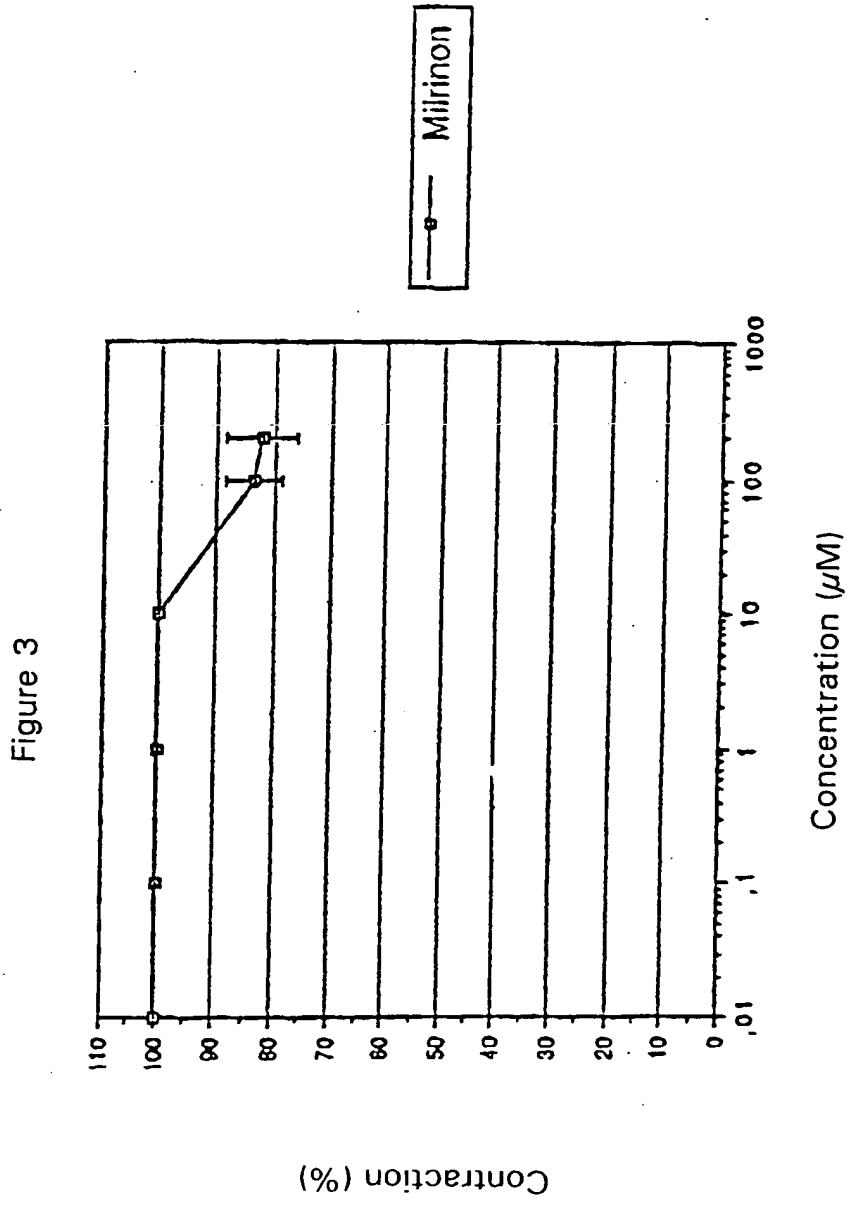
Figure 2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30
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Concentration (μM)
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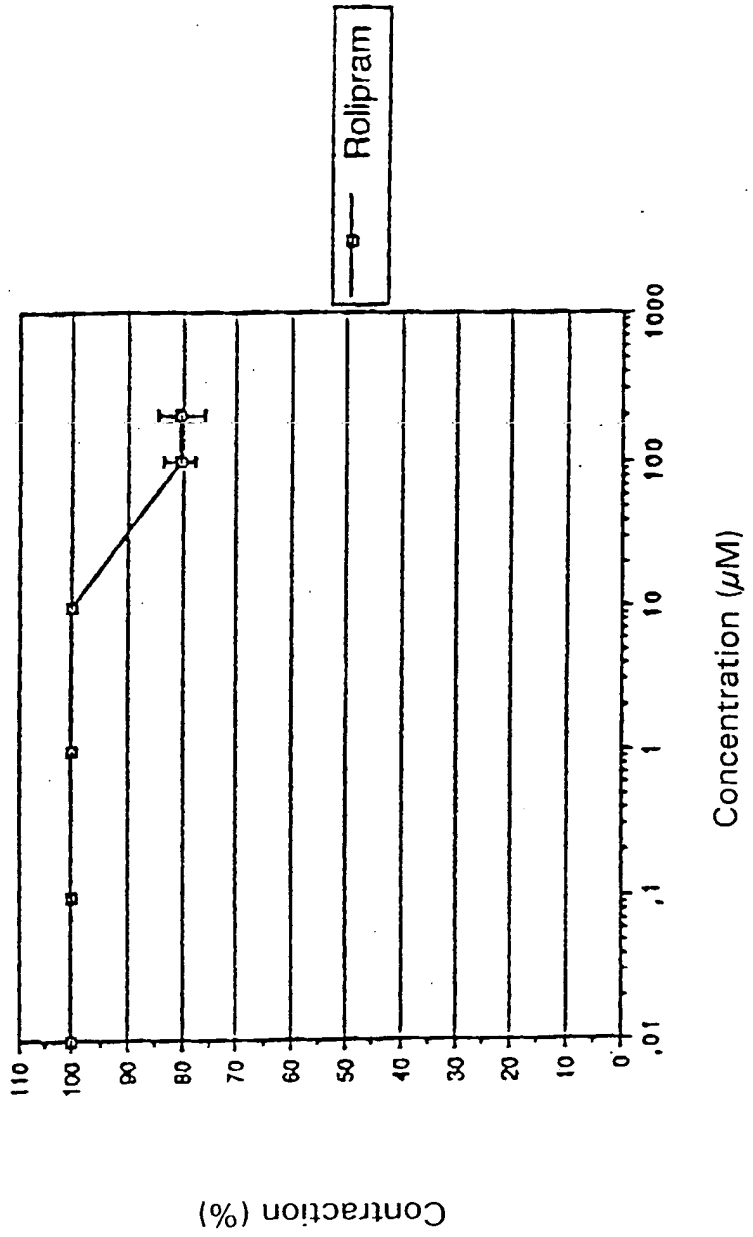
1
.1
.01

Figure 3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10
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,1
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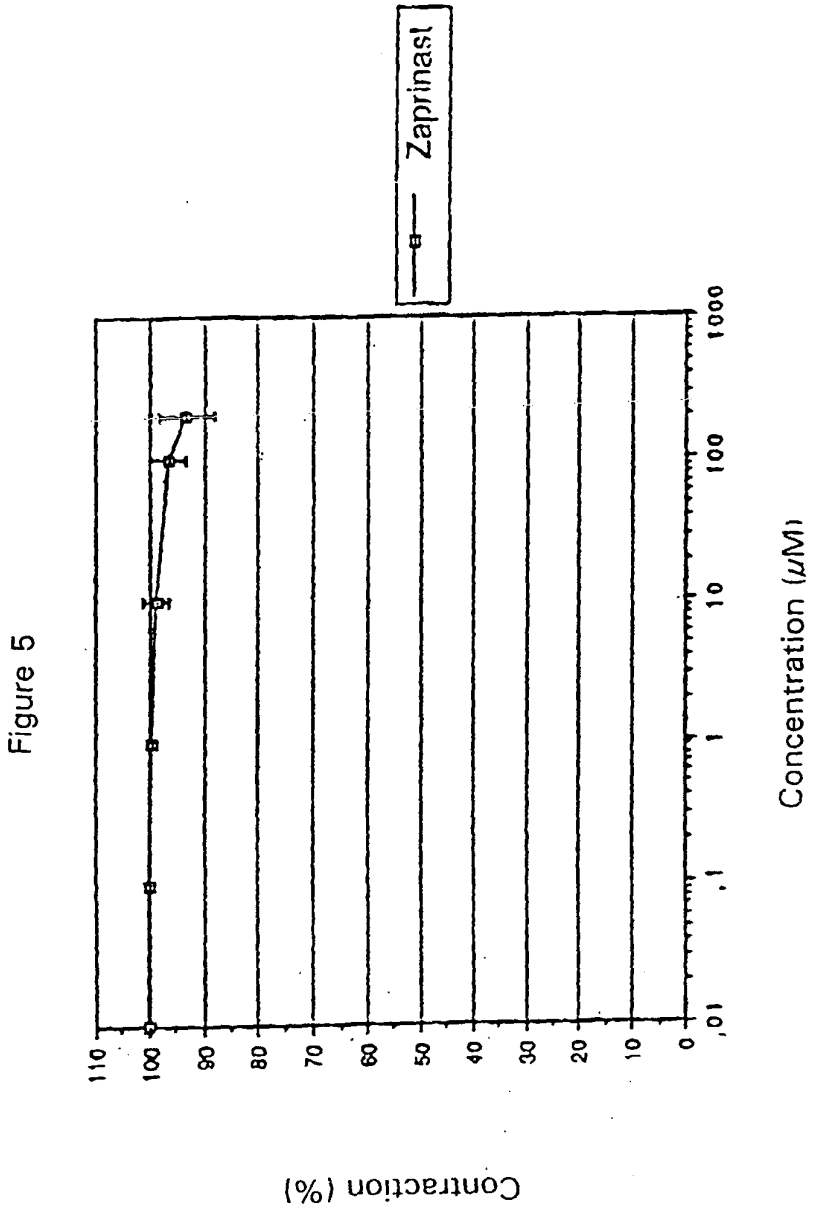
Figure 4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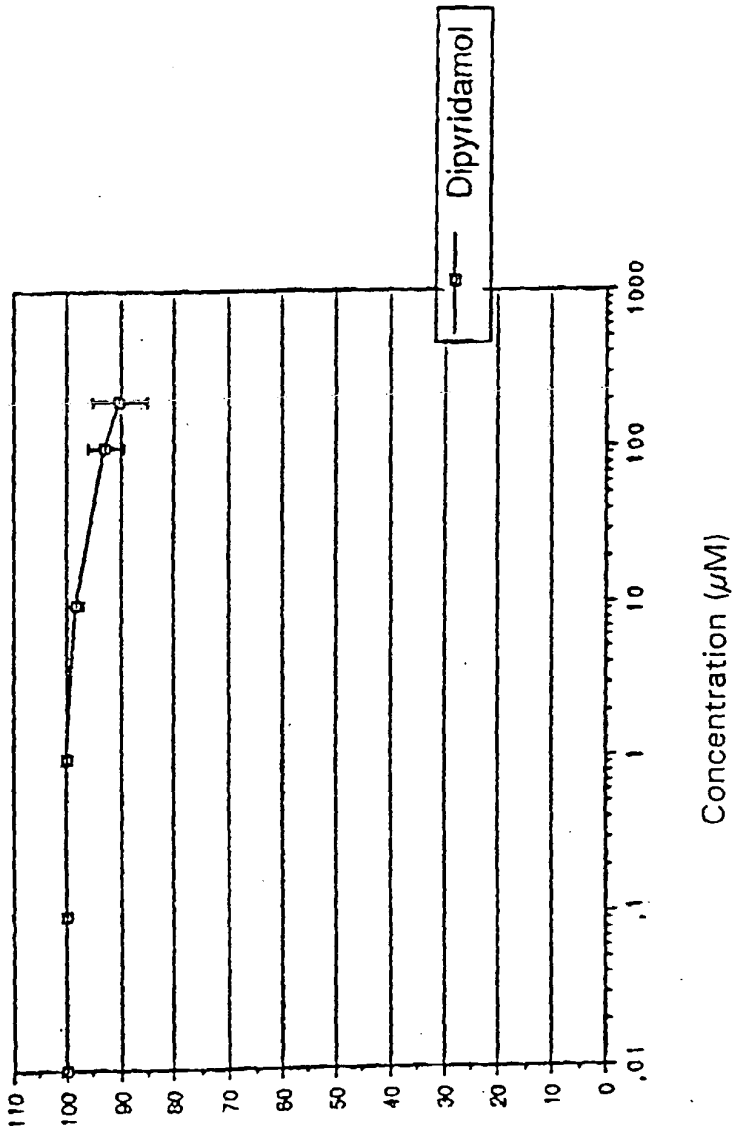
1000
Concentration (µM)

Figure 5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20
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Concentration (μM)
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.01

Figure 6

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/EP 96/03393

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435 A61K31/475 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP,A,0 722 944 (BAYER AG) 24 July 1996 * p.8, l.5, l.17; claims * ---	1,2,4,5
P,X	UROL RES, vol. 24, 1996, pages 129-34, XP000609239 TRUSS ET AL: "Cyclic nucleotide phosphodiesterase (PDE) isoenzymes in the human detrusor smooth muscle" * abstract; p.133, right hand col., last par. * --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1996	17. 01. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Uiber, P

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 96/03393

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	NEUROUROLOGY AND URODYNAMICS, vol. 15, January 1996, pages 59-70, XP000609243 TRUSS ET AL: "Effects of various phosphodiesterase-inhibitors, Forskolin, and sodium nitroprusside on porcine detrusor smooth muscle tonic response to muscarinergic stimulation and cyclic nucleotide levels in vitro" * abstract * ---	1-6
X	EP,A,0 546 547 (HOECHST JAPAN LTD) 16 June 1993 * p.2, l.5-12; claims 1-10 * ---	1,2,4,5
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